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10/517,028	06/15/2005	Evert Johannes Bunschoten	05558.0025.PCUS00	2857

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EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1654	

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10/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,028	BUNSCHOTEN ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-20* is/are pending in the application.

4a) Of the above claim(s) *14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-13 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/10/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-8 and 10-20 are pending; claims 14-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 24, 2007.

Claim Objections

2. Claims 1-8, 10-13 and 16-20 are objected to because of the following informalities: the Markush group of FSH substances in claim 1 is missing an "or" or "and"; and the Markush group of LH substances in claim 1 includes only one species. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The rejection of claims 1-13 and 16-20 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in light of the amendment filed 4/10/2008.

4. The rejection of claims 1-13 and 16-20 under 35 U.S.C. 112, second paragraph, is withdrawn in light of the amendment filed 4/10/2008.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 6-8, 10-13, 16-17, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grondahl, et al. (US 6,585,982) in view of Matthieu, et al. (US 2003/0092628) and further in view of Hideyuki Ikenaga, The Clinical Significance of the Ratio in FSH/LH of Human Menopausal Gonadotropins in a Programmed Stimulation Regimen for IVF-ET, Acta Obst. Gynaec. JPN, 1995, Vol. 47, No. 11, pp. 1223-1229 and Christina Bergh, Recombinant follicle stimulating hormone, Hum. Reprod., 1999, Vol. 14, No. 6, pp. 1418-1419.

Grondahl discloses that in vitro fertilization (IVF) [includes controlled ovarian hyperstimulation] of human oocytes has become commonly used for the treatment of female and male subfertility with the standard IVF treatment including a long phase of hormone stimulation of the female patient, e.g. 30 days, which is initiated by suppressing the patient's own follicle stimulating hormone (FSH) and luteinising hormone (LH) by gonadotropin releasing hormone (GnRH), and this is followed by injections of exogenous gonadotropins, e.g. FSH and/or LH in order to ensure development of multiple preovulatory follicles and aspiration of multiple in vivo matured oocytes immediately before ovulation and further, aspirated oocyte is subsequently fertilized in vitro and cultured, typically for 3 days before transferal back into the uterus at the 4-8 cell stage. Col. 1, lines 25-38. Grondal refers to the female cycle, as a way of performing IVF is as follows:

"Around day 21 in one cycle to around day 15 in the following cycle: The eggs are stimulated by treating the woman with GnRH, e.g. Synarel (400-600 micrograms per day).

Around days 6-16 in the second cycle: The eggs are stimulated by treating the woman with FSH, e.g. Gonal-F [FSH preparation], Puregon [recombinant FSH], or Humegon (hMG – a combination of FSH and LH] (150-400 IU per day). [a substance having follicle stimulating

hormone activity in an amount effective to stimulate multiple follicular development and includes a substance having luteinising hormone activity and it is in an amount effective to prevent or suppress symptoms of LH deficiency, which would result from administration of a gonadotropin releasing hormone antagonist as it is within the ranges disclosed by Applicants for this effect, i.e. between 1 and 40 IU recombinant LH per kg of body weight][1]

Around days 15-16 in the second cycle: The eggs are stimulated by treating the woman with hCG, e.g. Pregnyl or Profasi (2000-5000 IU per day)[followed by administration of a meiosis and luteinisation inducing substance in an amount effective to stimulate resupmtion of meiosis and luteinisation].

Around day 18 in the second cycle: The eggs are retrieved from the woman [harvesting one or more ova from mature ovarian follicles].

Around day 18-19 in the second cycle the eggs are maturated with a MAS compound in order to stimulate meiosis. In this additional maturation stem, step, the concentration of MAS compound may be in the range about 0.1-100 micromol per liter …

Around days 19-21 in the second cycle: The eggs are fertilized in vitro. …

Around day 21 in the second cycle: One or more embryos are transferred to the woman's uterus. Col. 2, lines 20-65.

[1] Women typically weigh between 42 to 120 kg. See, e.g. Womens average weight chart and percentile distribution - A weight chart for women of "White" race/ethnicity, showing – average weight changes with age, 2000, pp. 1-2, http://www.halls.md/chart/women-weight-w.htm; Women's Weight Chart for women of "Black" race/ethnicity, showing weight changes with age, 2000, pp. 1-2, http://www.halls.md/on/women-weight-b.htm; Women's Weight Chart for women of "Mexican-American" race/ethnicity, showing weight changes with age, 2000, pp. 1-2, http://www.halls.md/on/women-weight-h.htm; Women's Weight Chart for women of "Other" race/ethnicity, showing weight changes with age, 2000, pp. 1-2, http://www.halls.md/on/women-weight-o.htm. Thus, the range of administration would be 42 to 4800 IU of recombinant LH.or 84 to 1800 IU of recombinant LH and would be effective to maintain the females blood serum concentration of LH substances at a level equivalent to more than 1 I.U. per LH.

However, Grondal does not disclose that a gonadotropin releasing hormone antagonist is administered or that the LH can be recombinant LH. The examiner notes that the other limitations of claim 1 and 13 are met, as are the limitations of claims 2, 3, 6, 7, 8, 16 and 20 are met by the above disclosure. Because the amounts used and periods of time are encompassed by the above disclosure the compounds would have the same effects. The examiner also notes that the LH substance would be administered in an amount effective to maintain the females blood serum concentration of LH substances at a level equivalent to more than 1 I.U. LH/liter because the amount and the duration are within the specified ranges of dosing and this would implicitly cause the blood serum concentration to be more than 1.2 I.U. LH/liter.

Matthieu discloses GnRH antagonists and ganirelix, in particular, as compared to GnRH agonists,[2] in controlled ovarian hyperstimulation (COH) as well as to prevent premature LH surge, i.e. by GnRH receptor competition provide an immediate inhibition of gonadotropin secretion, especially of LH and thus, during COH by FSH, GnRH antagonist treatment is only required during the few days when there is an increased risk for a premature LH surge, noting that the GnRH antagonist dosage range is critical: too low a GnRH antagonist dosage leading to premature LH rises, while too high a GnRH antagonist dosage hampered follicular maturation with a dosing for human therapy a daily range is suggested for administration of the active ingredient between 0.001 and 5 mg/kg, preferably between 0.01 and 1 mg/kg. Col. 1 – [0001]-[0007]. The examiner notes that the average female weight is about 60 kg and this would definitely be at least 0.5 mg using the preferred range and heavier women would use the range of 0.8- greater than 4.0 mg ganirelix. Matthiem additionally discloses that the preparation is

administered parentally[3], together with FSH during the days of ovarian stimulation when a premature LH rise may easily occur, e.g. from day 5 of FSH administration onwards and administration is usually stopped when sufficient follicles have matured and exogenous hCG/LH is given for induction of ovulation, the amounts usually are 5000-10,000 IU, however, the exact regimen might depend on the individual response and is finally to be decided by the clinician who treats the subject, however, FSH treatment starts at menses day 1, 2, or 3and ovarian stimulation with FSH, preferable recombinant FSH, alone may be continued up to 5 days in an amount of e.g. 150-225 IU with treatment with GnRH antagonist, ganirelix, may be started at the first day of FSH but preferably such treatment starts at FSH treatment day 4 or 5 and may last 2-14 days, i.e. up to the moment whereupon the patient is treated with exogenous LH/hCG for ovulation induction. Cols. 1-2, [0009]-[0019], Examples, and claims 1-2 and 6-7. It would have been obvious to one of ordinary skill in the art at the time of the invention to have added the step of a gonadotropin releasing hormone antagonists, i.e. ganirelix, to the method of Grondal because the gonadotropin releasing antagonists prevent premature LH surge, thus allowing for maturation of more oocytes and the antagonists do not have the disadvantages associated with GnRH antagonists.

Ikenaga discloses a comparison of hMG preparation with different FSH/LH ratios to determine their clinical effectiveness in a programmed stimulation regimen for IVF-ET, where eighty-four IVF-ET candidates at Toho University Hospital received injections of an hMG preparation containing a 3:1 ratio of FSH/LH: Group A, 36 patients received hMG at an FSH/LH

[3] Noting the disadvantages with GnRH agonists, i.e. the initial flare-up and the rather long period until pituitary suppression becomes effective – usually patients undergoing COH start only treatment with (recombinant) FSH after 2 to 3 weeks pretreatment with GnRH agonists. Col. 1 - [0005].

1:1 ratio: Group B, and 20 patients received pure FSH: Group C - all received injections of 3000IU hMG daily for 7 days according to our COH protocol. Ikenage additionally discloses the results of the comparison was determined by analysis of serum levels of E2, number of mature follicles, number of retrieved oocytes, fertilization rate, cleavage rate, number of transferred embryos ad pregnancy rate. Ikenage further disclosed the results were as follows:

1. The serum E2 level was higher in Group A than in Croup C with significant differences.
2. The oocyte retrieval rate was significantly higher in Group A.
3. The rate of equally cleaved eggs was significantly higher in Group A.
4. The pregnancy rate was significantly higher in Group A.

Ikenaga concludes that an hMG preparation containing a 3:1 FSH/LH ratio was most suitable in our COH protocol. It would have been obvious to one of ordinary skill in the art at the time of the invention to have utilized a 3:1 ratio of FSH/LH in the combined method of Grondal and Matthiem to achieve a higher serum E2 level, higher oocyte retrieval rate, higher rate of equally cleaved eggs and a significantly higher pregnancy rate. Noting that the LH disclosed would be divided by 3.

Bergh discloses that recombinant gonadotrophin bear clear advantages in comparison with the older urinary preparations, i.e. guarantees high availability of a biochemically pure FSH [also holds true for LH] preparation free from urinary protein contaminants, which high purity and low immunogenicity allows s.c. administration. Bergh also discloses that recombinant FSH [also hold true for LH] advantageously provides constant availability batch to batch. Bergh concludes that the newly developed recombinant gonadotrophins have clear advantages,

[3] Preferably it is administered subcutaneously, particularly in the form of liquid solutions or suspension with glacial

particularly in purity, availability and batch consistency. It would have been obvious to one of ordinary skill in the art to make a recombinant FSH:LH in a three to one ratio in the combined method of Grondal and Matthiem to achieve better purity, availability and batch consistency of the FSH:LH and thus increase the serum E2 levels, increase the oocyte retrieval rate, increase the rate of equally cleaved eggs, and increase pregnancy rates. One would have had a reasonable expectation for success in administering a recombinant FSH:LH ratio of 3:1 in the combined method of Grondal and Matthiem, as these are the same compounds merely made recombinantly and with the dosage changed to 3:1, techniques widely practiced in the pharmaceutical arts, and because Ikenga discloses the specific advantages to such a ratio, while Bergh discloses specific advantages of making them recombinantly.

7. In the response filed, 4/10/2008, Applicant traverses the rejection on the grounds that prior art documents not relied upon in the 103 rejection teach away from the combination of Grondahl et al., Matthieu et al., Hideyuki Ikenaga, and Bergh. This is not persuasive because the references themselves together teach all claim limitations and provide motivation to combine. First, Applicant argues that Zelinski-Wooten et al. teaches that higher fertilization rates follow follicular stimulation with FSH alone than in the presence of FSH with LH. This argument is moot because the primary references relied upon in the rejection directly teaches the combination of FSH and LH in a successful method of IVF. Second, Applicant argues that WO 01/00227 discloses that pregnancy rates observed following COH protocols using GnRH antagonists are lower than the pregnancy rates observed following COH protocols using GnRH agonists because of an inhibitory effect of GnRH antagonists on implantation/pregnancy when administered at the

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acetic acid, mannitol, and water adjusted to pH5 with sodium hydroxide and/or hydrochloric acid. Col. 2, [0019].

concentration necessary to suppress premature LH surges. This is not persuasive. In paragraphs 0006-0008, Matthieu et al. acknowledge this potential problem and a solution to overcome it: "GnRH antagonists by GnRH receptor competition provide an immediate inhibition of gonadotropin secretion, especially of LH. Thus, during COH by FSH, GnRH antagonist treatment is only required during the few days when there is an increased risk for a premature LH surge. It has been found that the GnRH antagonist dosage range is critical: too low a GnRH antagonist dosage leading to premature LH rises, while too high a GnRH antagonist dosage hampered follicular maturation. For the antagonist ganirelix for example a fixed amount being at least 0.125 mg but less than 1 mg and preferably about 0.25 mg was suggested (WO98/58657). Surprisingly, however, it has now been found that there is no relationship between the implantation rate and level of LH (AUC), whereas there does exist a relationship between the GnRH antagonist levels (AUC) and the implantation rate. It has now been found that antagonist is to be administered in an amount depending on the body weight (BW)." Finally, Applicant cites meta-analysis studies that found that the inclusion of LH does not increase pregnancy rates. As stated above, this point is moot given that Grondahl et al. teach the combination of FSH and LH. The secondary reference Matthieu is relied upon to correct the deficiency in Grondahl regarding these use of a GnRH antagonist. Matthieu teaches the use of GnRH antagonists in controlled ovarian hyperstimulation to prevent premature LH surge.

8. Claims 1-8, 10-13, and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grondahl, et al. (US 6,585,982) in view of Matthieu, et al. (US 2003/0092628) and further in view of Hideyuki Ikenaga, The Clinical Significance of the Ratio in FSH/LH of Human Menopausal Gonadotropins in a Programmed Stimulation Regimen for IVF-ET, Acta Obst.

Gynaec. JPN, 1995, Vol. 47, No. 11, pp. 1223-1229 and Christina Bergh, Recombinant follicle stimulating hormone, Hum. Reprod., 1999, Vol. 14, No. 6, pp. 1418-1419 and further in view of Scott, et al., Correlation of Follicular Diameter with Oocyte recovery and Maturity at the Time of Transvaginal Follicular AspirationJournal of in Vitro Fertilization and Embryo Transfer, 1989, Vol. 6, No. 2, pp. 73-75.

Grondal, Matthieu, and Ikenaga disclose as set forth infra. However none of them disclose that the GnRH antagonist is administered when the largest developing ovarian follicle has reached an average diameter of 14 mm or 12 mm or 10 mm. Scott discloses that the probability of retrieving a metaphase I or II oocytes was significantly lower in follicles <11 mm and only somewhat higher in 12-14-mm follicles and equally high among the other groups and he concluded that follicles >15 mm provide the highest probability of retrieving mature oocytes and that metaphase I and metaphase II oocytes significantly outperform prophase I oocytes, even after controlling for fertilization. Pg. 73. Scott concludes that information regarding the probability of recovering oocytes in different maturational states has direct clinical relevance. Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to have administered the ganirelix when the oocytes were 10, 12 or 14 mm in the method of Grondal/Matthieu/Ikenga because you would want to optimize the number of oocytes that become greater than 15 mm by preventing a premature LH surge in order to obtain more metaphase I and metaphase II oocytes to get the better performance in your COH/IVF/ART.

Conclusion

9. No claims are allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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